

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number
WO 00/53191 A3

(51) International Patent Classification⁷: A61K 31/04. (31/195, 31/295, 31/70, 31/415, 31/535, 31/145, 31/40, 31/10, 38/44, 35/34, C12N 5/00)

(21) International Application Number: PCT/CA00/00255

(22) International Filing Date: 10 March 2000 (10.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/123,895 11 March 1999 (11.03.1999) US

(71) Applicant (for all designated States except US): THE UNIVERSITY OF MANITOBA [CA/CA]; Room 202, Administration Building, 66 Chancellors Circle, Winnipeg, Manitoba R3T 2N2 (CA).

(72) Inventor; and

(75) Inventor/Applicant (for US only): ANDERSON, Judy, E. [CA/CA]; 189 Kingsway Avenue, Winnipeg, Manitoba R3M 0G4 (CA).

(74) Agents: WHEELER, Michael, E. et al.; Smart & Biggar, 900-55 Metcalfe Street, P.O. Box 2999, Station D, Ottawa, Ontario K1P 5Y6 (CA).

(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
13 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



A3

(54) Title: MODULATION OF SKELETAL MUSCLE PRECURSOR CELL ACTIVATION

(57) Abstract: The present invention is directed to methods, pharmaceutical compositions and kits for modulating skeletal muscle precursor cell activation. Modulation is effected through the use of nitric oxide (NO), donors of NO, inhibitors of NO activity (NO inhibitor) or regulators of NO production, either locally or systemically. The invention further teaches the use of NO, an NO donor, an NO inhibitor or a regulator of NO production to modulate the effects of steroid hormone on skeletal muscle. The invention further provides a method for identifying a compound which effects a change in activation state of muscle precursor cells. A number of advantages is evident. By allowing skeletal muscle precursor cells to be manipulated directly, the invention enables specific treatments to regenerate and repair muscle, especially for the muscular dystrophies.

WO 00/53191

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/CA 00/00255

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/04 A61K31/195 A61K31/295 A61K31/70 A61K31/415
 A61K31/535 A61K31/145 A61K31/40 A61K31/10 A61K38/44
 A61K35/34 C12N5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ULIBARRI J A ET AL: "Nitric oxide stimulates myoblast proliferation in vitro." MEDICINE AND SCIENCE IN SPORTS AND EXERCISE, vol. 29, no. 5 SUPPL., 1997, page S228 XPG000961780 44th Annual Meeting of the American College of Sports Medicine; Denver, Colorado, USA; May 28-31, 1997 ISSN: 0195-9131 abstract --- -/-	1-12, 36, 40

 Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

1 December 2000

Date of mailing of the international search report

19.03.01^AName and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

Intern.	Application No
PCT/CA 00/00255	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US1993</p> <p>BAEK MI-YEONG ET AL: "Changes in the cellular cGMP levels and guanylate cyclase activities during chick myoblast fusion." Database accession no. PREV199396097003 XP002154299 abstract & KOREAN JOURNAL OF ZOOLOGY, vol. 36, no. 3, 1993, pages 433-438, ISSN: 0440-2510</p> <p>---</p>	1-9, 14-19, 36,37,40
X	<p>BREDT DAVID S: "NO skeletal muscle derived relaxing factor in Duchenne muscular dystrophy."</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 25, December 1998 (1998-12), pages 14592-14593, XP000960480 Dec., 1998 ISSN: 0027-8424</p> <p>page 14592, column 2, paragraph 3 -page 14593, column 1, paragraph 5</p> <p>---</p>	1
X	<p>SARKAR RAJABRATA ET AL: "Nitric oxide inhibition of endothelial cell mitogenesis and proliferation."</p> <p>SURGERY (ST LOUIS), vol. 118, no. 2, 1995, pages 274-279, XP000961764 ISSN: 0039-6060 abstract</p> <p>---</p>	1
X	<p>DATABASE WPI Section Ch, Week 199831 Derwent Publications Ltd., London, GB; Class B03, AN 1998-350696 XP002154301 & JP 10 120654 A (ONO PHARM CO LTD), 12 May 1998 (1998-05-12) abstract</p> <p>---</p> <p>-/-</p>	1

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/CA 00/00255

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 X	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US November 1997 (1997-11) LAMOSOVA D ET AL: "Influence of melatonin on chick skeletal muscle cell growth." Database accession no. PREV199800098087 XP002154300 abstract & COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY C PHARMACOLOGY TOXICOLOGY & vol. 118, no. 3, November 1997 (1997-11), pages 375-379, Nov., 1997 ISSN: 0742-8413</p> <p>---</p>	1
4 X	<p>AZZENA G B ET AL: "NITRIC OXIDE REGENERATES THE NORMAL COLONIC PERISTALTIC ACTIVITY IN MDX DYSTROPHIC MOUSE" NEUROSCIENCE LETTERS, LIMERICK, IE, vol. 261, no. 1/02, 1999, pages 9-12, XP000879028 ISSN: 0304-3940 the whole document</p> <p>---</p>	1-9, 14-19, 36,37, 39,40
1 X	<p>LEE KUN HO ET AL: "Nitric oxide as a messenger molecular for myoblast fusion." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 20, 1994, pages 14371-14374, XP002154298 ISSN: 0021-9258 abstract; figures 1,4 page 14372, column 2, paragraph 3</p> <p>---</p>	1-9, 14-19, 36,37,40
1 X	<p>YAN ZHONG-QUN ET AL: "Overexpression of inducible nitric oxide synthase by neointimal smooth muscle cells." CIRCULATION RESEARCH, vol. 82, no. 1, pages 21-29, XP000961767 ISSN: 0009-7330 abstract page 24, column 2, paragraph 5 -page 26, column 2, paragraph 1; figures 7,8 page 28, column 2, paragraphs 2,3</p> <p>---</p> <p>-/-</p>	1-9, 14-19, 36,37,40
3		

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/CA 00/00255

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
4 X	<p>HAYCOCK J W ET AL: "OXIDATIVE DAMAGE TO MUSCLE PROTEIN IN DUCHENNE MUSCULAR DYSTROPHY" NEUROREPORT, GB, RAPID COMMUNICATIONS OF OXFORD, OXFORD, vol. 8, no. 1, 1996, pages 357-361, XP000879014 ISSN: 0959-4965 abstract page 357, column 2, paragraph 2 -page 358, column 1, paragraph 1 page 361, column 1, paragraph 2 -column 2, paragraph 2</p> <p>---</p>	1-9, 14-19, 36,37, 39,40
1 X	<p>CHAO DANIEL S ET AL: "Selective loss of sarcolemmal nitric oxide synthase in becker muscular dystrophy." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 184, no. 2, 1996, pages 609-618, XP000961763 ISSN: 0022-1007 abstract page 610, column 1, paragraphs 2,3 table 1 page 616, column 2, paragraphs 2,3</p> <p>---</p>	1-9, 14-19, 36,37, 39,40
1 X	<p>AZZENA GIAN BATTISTA ET AL: "Nitric oxide regenerates the normal colonic peristaltic activity in mdx dystrophic mouse." NEUROSCIENCE LETTERS, vol. 261, no. 1-2, 12 February 1999 (1999-02-12), pages 9-12, XP000961771 ISSN: 0304-3940 abstract page 9, column 1 -page 10, column 1, paragraph 1 page 12, column 1</p> <p>---</p>	1-9, 14-19, 36,37, 39,40
3 X	<p>US 5 583 101 A (STAMLER JONATHAN ET AL) 10 December 1996 (1996-12-10)</p> <p>abstract; examples 1-6 column 1 -column 6, line 40 column 8, paragraph 2</p> <p>---</p> <p align="center">-/-</p>	1-9, 14-19, 36,37, 39,40
3		

INTERNATIONAL SEARCH REPORT

Internr Application No
PCT/CA 00/00255

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 A	SOHN YOON K ET AL: "Neuritic sprouting with aberrant expression of the nitric oxide synthase III gene in neurodegenerative diseases." JOURNAL OF THE NEUROLOGICAL SCIENCES, vol. 162, no. 2, 15 January 1999 (1999-01-15), pages 133-151, XP000961766 ISSN: 0022-510X the whole document ---	1-9, 14-19, 36,37, 39,40
3 A	WO 97 33173 A (UNIV CALIFORNIA) 12 September 1997 (1997-09-12) the whole document ---	1-40
6 P,X	KALIMAN, PERLA ET AL: "Insulin-like growth factor-II, phosphatidylinositol 3-kinase, nuclear factor-.kappa.B and inducible nitric-oxide synthase define a common myogenic signaling pathway" J. BIOL. CHEM. (1999), 274(25), 17437-17444, XP000960874 the whole document ---	1-9, 14-19, 36,37,40
6 A	EL-DADA, MANAR D. ET AL: "Involvement of nitric oxide in nicotinic receptor-mediated myopathy" J. PHARMACOL. EXP. THER. (1997), 281(3), 1463-1470, XP000972194 the whole document -----	1-40
3		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00255

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9, 14-19, 36, 37, 39, 40 (all partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/CA 00/00255

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
JP 10120654	A 12-05-1998	NONE			
US 5583101	A 10-12-1996	AU 3008395 A	16-02-1996		
		CA 2194991 A	01-02-1996		
		JP 10511075 T	27-10-1998		
		WO 9602241 A	01-02-1996		
		US 5545614 A	13-08-1996		
WO 9733173	A 12-09-1997	AU 2208097 A	22-09-1997		

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 August 2000 (31.08.2000)

PCT

(10) International Publication Number
WO 00/49993 A3

(51) International Patent Classification⁷: A61K 31/58, (81) Designated States (national): AE, AL, AM, AT, AU, AZ, C07J 5/00, 71/00, 17/00 BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(21) International Application Number: PCT/US00/04507

(22) International Filing Date: 23 February 2000 (23.02.2000)

(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
09/256,171 24 February 1999 (24.02.1999) US

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): NI-TROMED, INC. [US/US]; 12 Oak Park Drive, Bedford, MA 01730 (US).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

(72) Inventors; and

(75) Inventors/Applicants (for US only): GARVEY, David, S. [US/US]; 10 Grand Hill Drive, Dover, MA 02030 (US). WORCEL, Manuel [FR/US]; 20 Gloucester Street, No.4, Boston, MA 02115 (US).

(88) Date of publication of the international search report:
30 November 2000

(74) Agent: GRIEFF, Edward, D.; Hale and Dorr LLP, 1455 Pennsylvania Avenue, NW, Washington, DC 20004 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/49993 A3

(54) Title: NITROSATED AND NITROSYLATED STEROIDS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES AND DISORDERS

(57) Abstract: The present invention relates to nitrosated and/or nitrosylated steroids and to methods for the treatment of cardiovascular diseases and disorders, particularly the prophylactic and/or therapeutic treatment of restenosis, by administering nitrosated and/or nitrosylated steroids that are capable of releasing nitric oxide or indirectly delivering or transferring nitric oxide to targeted sites under physiological conditions. The methods for the treatment of cardiovascular diseases and disorders may further comprise administering at least one compound that donates, transfers, or releases nitric oxide and/or elevate endogenous nitric oxide or endothelium-derived relaxing factor *in vivo* and/or is a substrate for nitric oxide synthase.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04507

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/58; C07J 5/00, 71/0, 17/00.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/174, 178, 169, 177, 179, 180, 181, 182; 552/572, 573, 575, 565, 566, 276; 540/63, 66, 67, 69, 70, 114.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, CAPLUS, CAOLD

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,824,669 A (GARVEY et al) 20 October 1998, entire document.	1-8
A	US 5,837,698 A (TJOENG et al) 17 November 1998, entire document.	1-8
A, P	US 5,985,862 A (TJOENG et al) 16 November 1999, entire document.	1-8
A	US 5,792,758 A (TJOENG et al) 11 August 1998, entire document.	1-8

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 AUGUST 2000

Date of mailing of the international search report

22 SEP 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer

SABIHA QAZI

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/04507

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8, formula III

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04507

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/174, 178, 169, 177, 179, 180, 181, 182; 552/572, 573, 575, 565, 566, 276; 540/63, 66, 67, 69, 70, 114.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- I. Claims 1-8, formula III, drawn to method of use, when classified in class 514, subclass 169+.
- II. Claims 1-8, formula II, drawn to method of use, when R is methyl piperazine and is the only hetero group present in the compound, when classified in class 514, subclass 169+.
- III. Claims 1-8, formula IV, drawn to method of use, when classified in class 514, subclass 169+.
- IV. Claims 1-8, formula V, drawn to method of use, when R20 and R21 are H or hydroxy, classified in class 514, subclass 169+.
- V. Claims 1-8, formula VI, drawn to method of use, classified in class 514, subclass 169+.
- VI. Claims 1-8, formula I, drawn to method of use, when R1 represent H, a hydroxy, a nitrate ester, a nitrite ester, a thionitrile ester, a thionitrate ester and no hetero group is present in the compound, R2 and R3 represent H, a hydroxy group, a nitrate ester, nitrite ester, classified in class 514, subclass 169+.
- VII. Claims 25-26 drawn to method of direct delivery, classified in class 514, subclass 169+.
- VIII. Claims 27-29 drawn to method drawn to medical devices.
- IX. Claims 30 drawn to method drawn to medical devices.
- X. Claims 31 drawn to method drawn to medical devices.
- XI. Claims 32 and 33 drawn to prevention of platelet aggregation and platelet adhesion.
- XII. Claims 34 and 35 drawn to method of use.
- XIII. Claim 36-37 drawn to method of treating injured tissue of the compounds of formula (III).
- XIV. Claim 36-37 drawn to method of treating injured tissue of the compounds of formula (V).
- XV. Claim 36-37 drawn to method of treating injured tissue of the compounds of formula (VI).
- XVI. Claim 38-41 drawn to method of treating injured tissue of the compounds of formula (II).
- XVII. Claims 42-45 drawn to compounds of formula II, classified in class 552, subclass 540+.
- XVIII. Claims 42-45 drawn to compounds of formula II, classified in class 552, subclass 540+.
- XIX. Claims 42-45 drawn to compounds of formula I, drawn to method of use, when R1 represent H, a hydroxy, a nitrate ester, a nitrite ester, a thionitrile ester, a thionitrate ester and no hetero group is present in the compound, R2 and R3 represent H, a hydroxy group, a nitrate ester, nitrite ester, classified in class 552, subclass 540+.
- XX. Claims 42-45 drawn to compounds of formula II, when R is methyl piperazine and is the only hetero group present in the compound, when classified in class 552, subclass 540+.
- XXI. Claims 42-45 drawn to compounds of formula II, drawn to compound when R3 and R4 can form a dioxarane ring, classified in class 540, subclass 1+.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/04507

XXII. Claims 9 and 10 are drawn to methods of claim 1 further comprising administering to the patient at least one therapeutic agent, classified in class 514, subclass 169+.

XXIII. Claims 11-20 are drawn to methods of claim 1 further comprising at least one compound that donates transfers or release nitric oxides, classified in class 514, subclass 169.

XXIV. Claims 21-24 are drawn to composition comprising at least one nitrosylated or nitrosated steroid bound to matrix, classified in class 514, subclass 169+.

If applicants want to elect the invention other than those cited above, they may elect a species and Examiner will build a group as cited above of the subgenus falling in the species for examination.

The inventions listed as Groups I to XXIV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Instant claims are drawn to structurally dissimilar compounds with variety of substituents, their composition, different method of use, medical devices etc.

The claims herein lack unity of invention under PCT Rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 October 2000 (19.10.2000)

PCT

(10) International Publication Number
WO 00/61604 A3

(51) International Patent Classification⁷: C07J 41/00, (81) Designated States (national): AL, AU, BA, BB, BG, BR, A61K 31/575 CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

(21) International Application Number: PCT/EP00/03238

(22) International Filing Date: 11 April 2000 (11.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A000751 13 April 1999 (13.04.1999) IT

(71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).

(72) Inventor; and

(75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

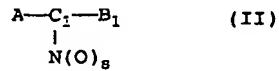
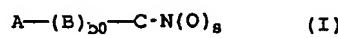
(88) Date of publication of the international search report:
15 March 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



(54) Title: PHARMACEUTICAL COMPOUNDS

WO 00/61604 A3



(57) Abstract: Steroidal compounds or their salts having general formulas (I) and (II) wherein: s is an integer equal to 1 or 2, preferably s = 2; b0 = 0 or 1; A = R-, wherein R is the steroidal drug radical, C and C₁ are two bivalent radicals. The precursors of the radicals B and B₁ are such as to meet the pharmacological tests reported in the description.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J41/00 A61K31/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 15568 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 16 April 1998 (1998-04-16) page 23, table examples 1,3 ----	1,2,4, 7-12
Y	WO 97 41144 A (SEARLE & CO ;TJOENG FOE S (US); CURRIE MARK G (US); ZUPEC MARK E () 6 November 1997 (1997-11-06) page 38, table page 4, paragraph 2; examples 21-26 ----	1,2,4, 7-12
A	WO 97 21721 A (SEARLE & CO ;TJOENG FOE S (US); CURRIE MARK G (US); ZUPEC MARK E () 19 June 1997 (1997-06-19) the whole document ----	1,2,4, 7-12 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search

21 November 2000

Date of mailing of the International search report

20.12.2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, P

INTERNATIONAL SEARCH REPORT

Internat. Appl. No
PCT/EP 00/03238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 436 936 A (HOECHST AG) 17 July 1991 (1991-07-17) page 2, line 11 - line 12; examples 1,2,42,43 ---	1,2,4, 7-12
Y	EP 0 290 885 A (CHIESI FARMA SPA) 17 November 1988 (1988-11-17) page 3, line 12 - line 15 table I, compound IV; table II, compound VII; table III, compounds IV and VII ---	1,2,4, 7-12
Y	CEDERQVIST B ET AL: "DIRECT DEMONSTRATION OF NO FORMATION IN VIVO FROM ORGANIC NITRITES AND NITRATES, AND CORRELATION TO EFFECTS ON BLOOD PRESSURE AND TO IN VITRO EFFECTS" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 47, no. 6, 1994, pages 1047-1053, XP000671053 ISSN: 0006-2952 page 1047, column 1, paragraph 2 -column 2, paragraph 1 ---	1,2,4, 7-12
Y	PATENT ABSTRACTS OF JAPAN vol. 007, no. 131 (C-169), 8 June 1983 (1983-06-08) & JP 58 045724 A (ORIZA YUKA KK), 17 March 1983 (1983-03-17) abstract ---	1,2,4, 7-12
Y	DE 196 34 793 A (SANOL ARZNEI SCHWARZ GMBH) 5 March 1998 (1998-03-05) page 2, line 2 - line 20; examples 1-3,5,7,8 ---	1,2,4, 7-12
Y	WO 88 00202 A (UNIV LOUIS PASTEUR DE STRASBOUR) 14 January 1988 (1988-01-14) page 6, paragraphs 3,5 page 9, line 5 - line 9 ---	1,2,4, 7-12
Y	US 3 702 335 A (LAFILLE CLAUDE) 7 November 1972 (1972-11-07) column 10, paragraph 1; example 10 ---	1,2,4, 7-12
Y	CHEMICAL ABSTRACTS, vol. 118, no. 17, 26 April 1993 (1993-04-26) Columbus, Ohio, US; abstract no. 169434, HORI, KIMIHIKO ET AL: "21-Substituted steroids" XP002153479 abstract & JP 04 273892 A (KAO CORP., JAPAN) 30 September 1992 (1992-09-30) ---	1,2,4, 7-12

-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CHEMICAL ABSTRACTS, vol. 130, no. 21, 24 May 1999 (1999-05-24) Columbus, Ohio, US; abstract no. 276039, BONN, R. ET AL: "SP/W-5186: a novel sulphydryl-containing NO donor" XP002153480 abstract & CARDIOVASC. DRUG REV. (1998), 16(3), 195-211 , -----</p>	1,2,4, 7-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/03238

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1,2,4,7-12 (partially searched) 3,5,6 (not searched) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,4,7-12 (partially searched) 3,5,6 (not searched)

Please note that the subject matter searched in the context of the present application is limited both under according to Art.17(2)(a)(ii) PCT (for the reasons given below) and according to Art.17(3)(a) PCT (due to a lack of unity the reasons for which are given separately).

Present claims 1-12 relate to an extremely large number of possible compounds and pharmaceutical compositions and uses thereof. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Furthermore, present claims 1-12 relate to compounds defined by reference to a desirable characteristic or property, namely the compounds are defined such that they attain a certain level of anti-oxidative activity evidenced according to test 4 or test 5 (both of which are elucidated in claim 1). Since this property (anti-oxidative activity) is in fact the problem to be solved by the compounds of the present application (see page 6, lines 2-7 of the description) - this means that the claimed compounds are defined in terms of their being a solution to this problem. It does not matter that there is also a generic Markush structural formula giving some degree of structural definition to the claimed compounds because the scope of this structural definition is extremely broad in terms of structural features (see above) the restriction of this very broad set of compounds by means of the desideratum is effectively the allegedly characterising feature of the claims (in particular independent compound claim 1) and so the technical meaning of this desideratum is essential in establishing the true scope of the claim according to Art.6 PCT. Since the skilled person is given no idea as to how to limit the broad scope of the compounds of claim 1 (and the uses and compositions thereof according to claims 10-12) to compounds which actually solve this problem, he must by necessity employ an inventive step according to Art.33(3) PCT in order to move from the disclosure of the claimed invention as given in claim 1 (and the uses and compositions thereof according to claims 10-12) to a viable product which actually solves this problem. Consequently the compounds of claim 1 are insufficiently disclosed according to Art.5 PCT to such an extent that no meaningful search is possible based on the full scope of claim 1.

Furthermore, the claims cover all compounds (claim 1) and uses and compositions (claims 10-12) having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds (and their uses and compositions). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific compounds of the examples and their uses and compositions thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,4,7-12 (in part)

Compounds of examples 1 and 2 - being the 3-(4-nitrooxy)-nbutyl ester of ursodeoxycholyl-ferulate and chenodesoxycholyl-ferulate respectively, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

2. Claims: 1,2,4,7-12 (in part)

Compounds of examples 3-5 being:-

Example 3

(11.beta.)
11,17-Dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyl oxy!-pregna-1,4-diene-3,20-dione

Example 4

(11.beta.)
11,17-Dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyl oxy!-pregna-4-ene-3,20-dione

Example 5

(11.beta., 16.alpha.)
9-Fluoro-11,17-dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyl oxy!-16-methylpregna-1,4-dien-3,20-dione

, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

INTERNATIONAL SEARCH REPORT

Information on patent family members				International Application No	
Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9815568	A	16-04-1998	IT AU AU BR CN EP HU	MI962048 A 719250 B 4780397 A 9711586 A 1253563 A 0929565 A 9904149 A	06-04-1998 04-05-2000 05-05-1998 24-08-1999 17-05-2000 21-07-1999 28-04-2000
WO 9741144	A	06-11-1997	US AU EP JP	5837698 A 2922797 A 0900233 A 2000509072 T	17-11-1998 19-11-1997 10-03-1999 18-07-2000
WO 9721721	A	19-06-1997	US AT AU CA DE DE EP	5707984 A 195128 T 1277297 A 2239910 A 69609632 D 69609632 T 0873351 A	13-01-1998 15-08-2000 03-07-1997 19-06-1997 07-09-2000 09-11-2000 28-10-1998
EP 0436936	A	17-07-1991	DE AU AU AU AU CA HU JP NO NZ PT US US ZA	4000397 A 660248 B 6189294 A 652928 B 6921791 A 2033755 A 210905 B 4331284 A 910075 A 236709 A 96438 A, B 5508275 A 5318987 A 9100132 A	11-07-1991 15-06-1995 21-07-1994 15-09-1994 05-09-1991 10-07-1991 28-09-1995 19-11-1992 10-07-1991 25-11-1992 15-10-1991 16-04-1996 07-06-1994 30-10-1991
EP 0290885	A	17-11-1988	IT JP US	1204571 B 63297383 A 4956384 A	10-03-1989 05-12-1988 11-09-1990
JP 58045724	A	17-03-1983	NONE		
DE 19634793	A	05-03-1998	NONE		
WO 8800202	A	14-01-1988	FR AT DE DE EP JP JP US	2600653 A 88479 T 3785505 A 3785505 T 0254655 A 1500430 T 2667418 B 4913852 A	31-12-1987 15-05-1993 27-05-1993 28-10-1993 27-01-1988 16-02-1989 27-10-1997 03-04-1990
US 3702335	A	07-11-1972	FR BE CA DE ES	2077750 A 762732 A 939335 A 2100475 A 387707 A	05-11-1971 16-07-1971 01-01-1974 02-09-1971 16-05-1973

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/03238

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3702335 A		GB 1324911 A	25-07-1973
JP 4273892 A	30-09-1992	NONE	